American Red Cross

Together, we can save a life

December 28, 2005

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Collection of Platelets by Automated Methods; Draft Guidance [70 FR 57609-57610, October 3, 2005; Docket No. 2005D-0330]

Dear Docket Officer:

The American Red Cross (Red Cross) appreciates this opportunity to provide comments concerning the Food and Drug Administration's (FDA or Agency) draft guidance titled "Collection of Platelets by Automated Methods" (Hereafter, referred to as the "Draft Guidance").

The Red Cross has been engaged in the collection of Platelets by automated methods for over 15 years. More than 160 Red Cross facilities are currently registered to collect Platelets by automated methods. In calendar year 2004, 97,411 Red Cross donors made 437,015 donation appointments, resulting in 638,971 Platelet components collected. More detailed information about Red Cross' experience with the process of plateletpheresis, and data regarding donation of multiple components, appears below.

We offer the following comments for your consideration. We have organized our remarks to first present and detail (in order of importance) the issues that have the greatest potential to impact donor safety or product safety, purity or potency, and availability of apheresis platelets. Following these comments, we have summarized comments of lesser, but important, impact in Attachment 1 (page 10, below).

The rationale for the requirement to limit donors to 24 components per year and the requirement to restrict intervals between multi-component donations is not evident. (III.B.2)

The proposed Guidance to limit plateletpheresis donations to a maximum of 24 Platelets, Pheresis components in a 12 month period and limit the interdonation interval based upon procedural yield may create significant platelet supply deficits and harm patients. Restricted to 24 component collections per donor per

year, the American Red Cross would have been prevented from collecting 35,786 products (~6% of its distributable inventory) from high-frequency, high-yield donors in calendar year 2004 and would have needed to increase its donation base by approximately 6% in an attempt to compensate. Additional product losses from donor dissatisfaction resulting from increasingly complex scheduling requirements at busy donor centers may exacerbate platelet deficits throughout the system.

Extensive experience under the 1988 Guidance allowing 24 collections per year in concert with donor deferral for counts $\leq$150,000/μL has established the safety of the current maximum component number and frequency of platelet collection. The American Red Cross has evaluated changes in donor platelet counts for individuals undergoing plateletpheresis over 1 to 8 years and component frequencies ranging from ~4 to 45 per year. Two separate analyses were conducted. The second study, in particular, evaluated changes in the platelet counts of donors who donated at least 20 times in 2002 and continued donating through October 2005. An extensive data summary is included in the addendum to this letter. Significant conclusions from two separate analyses were:

1. There is no statistically significant relationship between the changes in donor platelet counts with repeated apheresis procedures and the number of platelet products donated each year.

2. A minority of donors experienced modest platelet count decrements in the course of repeated procedures. Another small group of donors sustained an equal but opposite increase in their platelet count. It is unclear whether these changes in platelet counts are related to apheresis, represent a true change in circulating platelet mass (mean platelet volume [MPV] values were unavailable), or have any long-term hematological significance.

There is certainly a need to study the long-term consequences of plateletpheresis in frequent donors. However, given the lack of published evidence demonstrating harm or refuting the safety of long-term repeated platelet donation, Red Cross recommends that FDA sponsor a workshop on this subject and encourage the accumulation of prospective data prior to setting unnecessarily restrictive guidance that would negatively impact platelet availability and patient safety.

The Red Cross has been engaged in design and development of processes to collect triple Platelet components by automated methods, but has not yet implemented the program. Strategic planning for this project suggests that Red Cross could increase collections by as much as 36,000 additional Platelet components per year. The source of these additional components would

primarily be from current double component donors. Although it is not yet known whether these predictions will prove to be accurate, it is apparent that the proposed Draft guidance in its current form would adversely impact the yield of this program so that none of the anticipated increased availability will be realized.

The rationale for the requirement that a physician should be "present on the premises" and able to arrive at the collection site within 15 minutes is unclear. (III.D.)

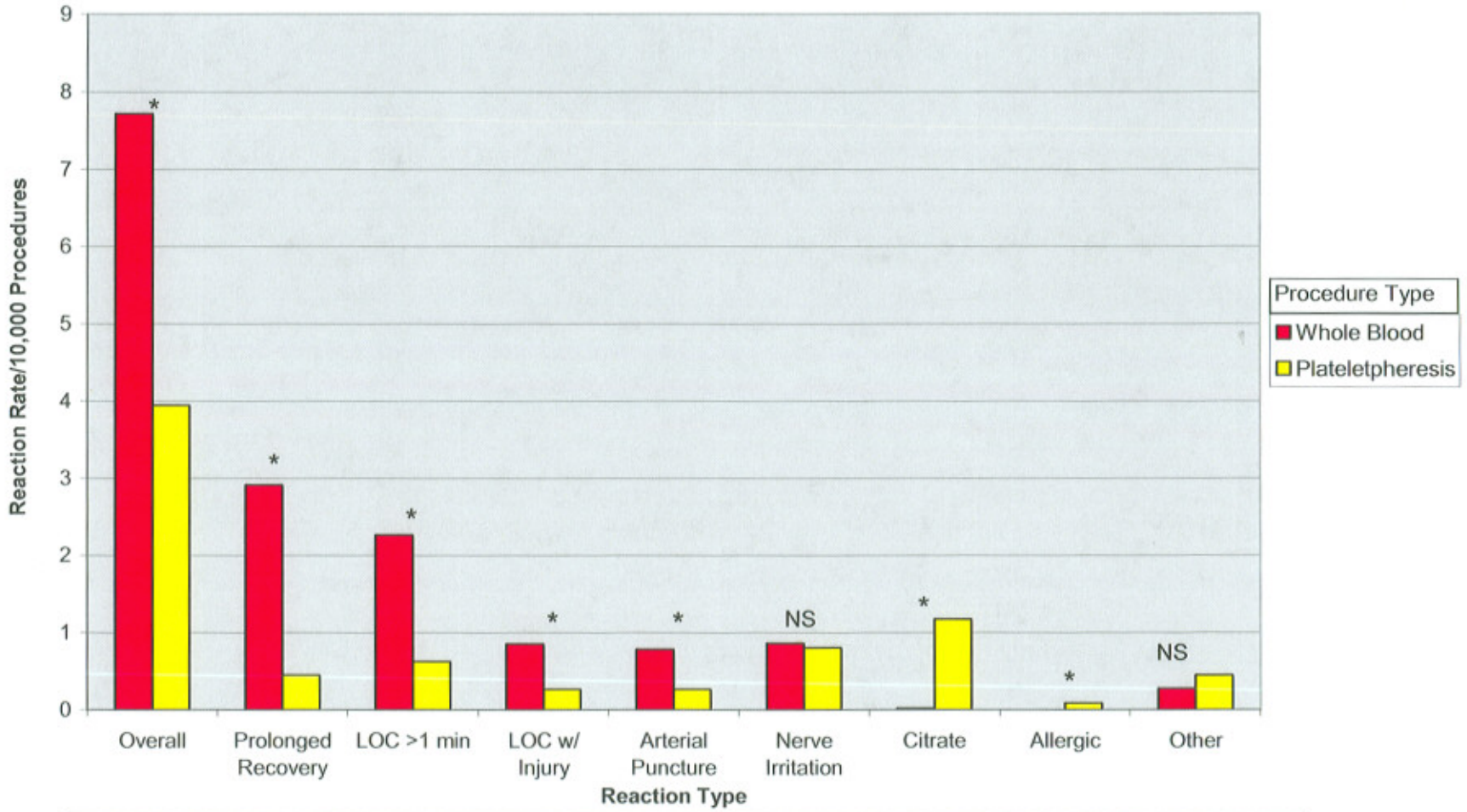
This requirement is unnecessarily restrictive and would not provide increased donor safety. Existing safeguards currently in place at donor centers adequately protect plateletpheresis donors. The data below supports the conclusion that plateletpheresis does not involve significantly more risk of serious adverse reactions than whole blood donations.

Donation of whole blood and apheresis platelets are rarely associated with major adverse reactions. Overall, major reactions occur at the collection site at a rate of 8 of 10,000 venipunctures for whole blood donation, and 4 of 10,000 venipunctures for automated collections (Figure 1). The higher overall rate of major reactions during whole blood collections compared to plateletpheresis is statistically significant. The only types of major reactions that occur at higher rates in plateletpheresis donors are citrate reactions, allergic reactions (Figure 1) and hematomas (not shown).

Apheresis technology has improved to provide a simpler process and safer machines for collection procedures today compared to those performed in the past. Extracorporeal volume is less than a unit of whole blood. Citrate administration is monitored by the instrument. Solutions (e.g., citrate and saline) are either an integral part of the disposable kit or used through compatible or color coded connections, which significantly reduce the potential for operator error in setting up the machine.

Instrument operation has been simplified with "easy-to-read" touch screens that facilitate operation of the instrument and reduce the potential for error by limiting the number of options and settings available to the operator. Many suppliers are avoiding the use of latex in disposables and the use of ethylene oxide to sterilize the kits. All these factors have improved the safety for the donor, making major adverse reactions to the procedure uncommon. Simply stated, plateletpheresis donors are not at greater risk of serious medical complications than whole blood donors.

Figure 1: Major Donor Reactions during Whole Blood and Plateletpheresis Procedures (July 05 through September 05)



*Difference between reaction rates for WB and apheresis collections are statistically significant using Chi Square/Fisher's Exact Test. For all comparisons, $p<0.05$, except those denoted NS, not significant.
LOC, loss of consciousness
Total number of procedures in July -September 2005: Whole blood, 1,633,388; plateletpheresis, 119,260.

Donor reactions can be managed safely and effectively by trained staff at the collection site, with a physician in contact with the collection center by telephone. Collections staff are trained in providing immediate care to donors experiencing reactions and at least one collection staff member trained in CPR is present on the premises at all times. Collections staff cannot wait for help to arrive before responding to acute life-threatening emergencies such as anaphylaxis, and would be expected to provide immediate care such as using an EpiPen. In the event of a serious, life-threatening reaction, the most appropriate response would be to provide immediate care and call Emergency Medical Services (e.g., 911) who are better equipped than an individual physician for resuscitative efforts.

The requirement to have a physician on the premises could have the unintended consequence of reducing the number of collection facilities, and would be predicted to further decrease collection and availability of Platelets, Pheresis.

The guidance requirements regarding the deferral of donors for ingestion of drugs that affect platelet function is not consistent with other FDA/CBER guidance. (III.A.)

In general, the new deferral requirements for medications that affect platelet function are not supported with an adequate rationale. The use of the Armed Services Blood Program Office (ASBPO) medication deferral criteria as a basis for recommendations is not appropriate, the methodology that was used to develop the criteria is not disclosed in the document, the criteria likely reflect the opinions of one group of physicians, and alternate criteria have been developed by many other blood centers. The need for a document like the ASBPO Medication Deferral List is questionable because only a short list of medications are mandatory deferrals and the vast majority of medications do not present a risk to either donor or recipient safety.

The requirement for a 5 day deferral for aspirin (ASA) is inconsistent with the current AABB Standards which only requires 36 hour deferral after the last dose of aspirin. The rationale to support the 36 hour deferral includes the published report of Stuart et al.[1] which demonstrated that the prolonged bleeding times were corrected to normal in recipients of platelets from donors who had taken aspirin 36 hours before donation.

The rationale for the requirement for deferral for NSAIDS (3 days from last dose) is not clear. Currently AABB standards do not require deferral for medications that reversibly inhibit platelet function. Nonaspirin NSAIDs

[1] Stuart et al. New Engl J Med 287:1105-1109; 1972.

cause transient, dose-dependent and modest bleeding time abnormalities; however, these abnormalities usually do not exceed the upper limit of normal.[2]

The rationale for the requirement for deferral for Plavix and Ticlid (5 days and 14 days, respectively, from the last dose) is not clear. Red Cross currently defers donors for 7 days for use of either Plavix or Ticlid. These drugs irreversibly inhibit platelet function, but are rapidly metabolized. Nearly complete platelet turnover is achieved over a 7-8 day period, and, published reports have demonstrated that platelet function and bleeding time return to normal within 4-8 days after the last does of the drugs.[3] Consequently, a 7 day deferral period is appropriate for both Ticlid and Plavix and is an interval that will facilitate donor recall.

The requirement to perform a White Blood Cell (WBC) count prior to the first donation is unnecessary. (III.A.)

Newer technologies are highly efficient at separating WBCs from platelets. Routinely, a maximum of 5×10^6 leukocytes are removed from the donor per collection. This represents a negligible fraction of total body leukocytes that is removed with each procedure. There is likely no physiologic consequence to this extent of WBC removal. The WBC count is not necessary to assess donor eligibility, because other criteria (e.g., donor temperature, health history) are adequate to protect both donor and recipient safety. There is no manufacturer's requirement to monitor WBC count. FDA itself seems uncertain of the value of the initial WBC count, since it allows a post-collection count to be substituted. The draft guidance does not contain advice about how to manage this information or how the information on WBC counts should be used in determining donor eligibility. The requirement for initial WBC count is not useful and should be removed.

The intent of the requirement to perform bacterial testing on 500 collections during product performance qualification is unclear. (VI.D.)

The intent of this requirement is not clear with respect to whether it applies to ongoing performance, or for a new facility/system performance qualification. The rationale for introducing this requirement is not clear and it is not stated whether it is based on scientific data from industry survey or a statistical rationale from FDA as a minimum requirement. In interpreting the FDA's draft guidance definition of a failure, it is not clear if the intention was to include false positive results as failures, or not.

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2 Schafer, J Clin Pharmacol 35:209-19; 1995.

3 Patrono et. al., Chest 119:39-63; 2001.
Komatsu T, et. al., J Gastroenterol 40:698 – 707; 2005.

ARC (and most, if not all other, plateletpheresis establishments) tests 100% of units collected and all of the products that test positive, false positive or indeterminate are discarded. The following year-to-date data demonstrates our process performance. Based on the following ARC data, would FDA consider these to be a failure?

ARC bacterial Detection Testing rate (1/1/05 – 10/31/05, n = 350,840)

• True Positive	20.0 / 100K	or	1:5,012
• False Positive	38.8 / 100K	or	1:2,580
• Indeterminate	7.1 / 100K	or	1:14,034
• Total Positive	65.9 / 100K	or	1:1,519

The requirement for 500 negative cultures would only delay qualification of platelet products without adding additional safety or assurance of product purity. All products are cultured before release and most positive results obtained with bacterial testing are unrelated to the actual apheresis collection procedure; therefore, Red Cross recommends that consideration be given to eliminating the requirement for bacterial testing for product performance qualification.

The rationale for lower limits for total volume loss per collection procedure is not provided. (III.B.4)

The rationale/justification for the requirement that volumes "should not exceed 500 mL (600 mL for donors weighing 175 lbs or greater)" while collection device manufacturers currently have 510(k) clearance for greater volumes is not provided. For donor safety, the volume removed should not exceed 15% of blood volume. Manufacturer's approved maximum volume and donor weight should be the determining factors for the collection volume that can be safely removed.

The guidance recommendation to utilize "scan statistics" for QC monitoring requires further explanation. (VII.C.2)

The Draft Guidance raises many questions about the use of scan statistics. Red Cross has the following concerns:

- What parameters would be measured as part of the more extensive QC monitoring program?
- Overall, how would scan statistics be applied, considering the numerous sites and device types that are in use to collect Platelets, Pheresis?
- Is the recommendation for random selection of 10% of annual collections a requirement, or an example of a plan?

- It would be useful for FDA to provide additional justification for the use of a system like scan statistics that will increase QC Monitoring substantially. Please refer to the final comment below that recommends a public workshop. ARC believes that such a workshop would be an appropriate venue for FDA to propose and publicly discuss a planned revision of the 640.25(b)-Quality Control Testing requirements section based on lessons learned from industry experience with current technological advances for collection of Platelets by automated methods.

FDA should convene a public workshop to collect stakeholder input into the requirements for collection and manufacture of Platelets by automated methods.

Plateletpheresis is an efficient and reliable collection process which produces a high quality, safe and efficacious platelet component for transfusion. Accumulated and extensive experience with collecting platelets by apheresis has shown that the process is well tolerated by donors and is as safe, if not safer for the donor, than whole blood donation. Yet it appears that the Agency feels more stringent guidance is needed for a highly automated process with relatively few problems.

The blood collection industry commands a wealth of medical knowledge and practical experience relating to the collection, processing, testing, labeling, storage, and distribution of Platelets, Pheresis. It is ARC's belief that an open discussion of scientific rationale, medical concerns, and practical considerations in a public forum would provide the best approach for FDA to reach consensus and incorporate industry "best practices" in a finalized guidance document. Although the current 90-day comment period could be extended, ARC believes that a dialogue among all stakeholders, similar to that utilized for Docket #2003N-0211 ("Revision to Labeling and Storage Requirements for Blood and Blood Components, Including Source Plasma") is the most effective alternative for improving the guidance. ARC believes that the impact of this guidance is of comparable magnitude.

The Red Cross understands and appreciates that financial considerations alone are not sufficient reasons to determine when, how, and what changes should be made to the manufacturing process of plateletpheresis units (or any blood component). However, we do believe that this information is relevant and may be useful as the FDA develops this guidance document; therefore we would like to provide FDA with an estimate of the financial impact of this Draft Guidance as it is proposed. Our estimates are still preliminary, yet conservative, based upon assumptions that may change.

In estimating the net financial impact arising from this guidance, the Red Cross evaluated the additional costs associated with the following four items:

- Donations limited to 24 platelet products/year/donor
- Physician required to be on site at each location where platelets are collected by apheresis
- NSAID deferrals instituted for 3 days from the last dose
- New limits on volume loss per collection procedure

The Red Cross estimates that these four requirements alone could potentially result in decreased platelet supply on the order of a loss of more than 65,000 Platelet Pheresis components unless additional donor recruitment is successful and $40 million per year in additional cost and lost margin.

Please refer to the Attachments 1 and 2 for additional comments. The comments in Attachment 1 do not have the level of impact as the comments above; however, they do require clarification in order to make the draft more effective.

The Red Cross appreciates this opportunity to provide public comments on the Draft Guidance. If you have any further questions or require follow-up, please contact Richard S. Robinson, Regulatory Affairs, at 202-303-5867 (phone), 202-303-0190 (fax) or RobinsonR@usa.redcross.org (e-mail).

Sincerely,

C.William Cherry
Senior Vice President
Quality and Regulatory Affairs

for Jerry Squires, M.D., Ph.D.
Chief Medical Officer

Attachment 1: "Additional Comments Regarding Draft Guidance"
Attachment 2: "Long-Term Plateletpheresis and Donor Platelet Counts"

ADDITIONAL COMMENTS REGARDING DRAFT GUIDANCE

Section III: DONOR SELECTION AND MANAGEMENT

- In section III, there are multiple references to obtaining a post-donation platelet count (e.g., III.A. third bullet; III.B.1.second bullet; III 2. sixth bullet). A post-donation platelet count is not necessary, and has no value in qualifying a donor and no role in ensuring the safety of the donor. For donor qualification, a more effective approach is to use the previous pre-donation count which would more accurately reflect the donor's baseline platelet count.
- Section III, B.1.second bullet states that only a single Platelets, Pheresis should be collected from first time donors who do not have a pre-donation platelet count. However, first-time donors should be allowed to donate Plasma or Red Blood Cells in addition to a single Platelets, Pheresis component if appropriately qualified for donation. (Page 5)
- Section III. B.1.third bullet requires a subsequent platelet count before collecting a donor whose platelet count is less than 150,000/uL. However, there should be an option to defer donors with platelet counts below 150,000/ul for 8 weeks and treat the individual as a new donor when they present again to donate. Most platelet counts below 150,000/uL on repeated donors are spurious results due to pre-analytical variables such as platelet clumping in the sample and are not repeated on subsequent donations. However if the donor's platelet count tests below 150,000/uL on two consecutive donations it is reasonable to require a count of greater than 150,000/uL before donating. (Page 6)
- Currently there is no requirement to wait 7 days following the donation of double Platelets, Pheresis or 14 days following the donation of triple Platelets, Pheresis. These intervals are arbitrary and unnecessary because donors are qualified on the day of donation. (Sec. III. B. 2.)
- Since many Whole Blood collections are 500 mL rather than 450 mL, the reference to 450 mL is confusing and should be eliminated. (Sec. III. B. 3.)

Section IV: INFORMATION PROVIDED TO THE DONOR

- Informing the donor of the number of Whole Blood, apheresis Red Blood Cells, and plateletpheresis procedures the donor may undergo is unnecessary and potentially confusing for the donor given the different possible combinations of collection procedures. FDA requires Red Cross to stringently monitor this frequency for each donor; it is highly unlikely that the donor will keep a more accurate record.

Section V: COMPONENT COLLECTION AND MANAGEMENT

- The basis for setting the requirements for target yields for double and triple components in the Guidance document is not clear. The yield in the final product should determine whether the product is a double or triple. In addition each donor is different and the target yield for collection should be determined on what is necessary for obtaining a successful collection. (Sec. V. B.)

Section VI: PROCESS VALIDATION

- The introductory paragraph makes reference to the 1987 "Guidance on General Principles of Process Validation," but the terms describing the elements of Process Validation in this draft are inconsistent with the referenced guidance. (Sec. VI. Introduction)
- It is not clear if the use of the term "blood cell counting devices …used to determine the residual WBC count" also refers to the Nageotte cell counting chamber. The Nageotte chamber itself cannot be validated, only inspected for damage. FDA should make available a list of hematology devices cleared for this purpose. (Sec. VI. Introduction)
- Scales and pH meters can be standardized and qualified, but this is not process validation. (Sec. VI. Introduction)
- Reference to nitrazine paper on page 15 apparently contradicts the recommended testing technique on page 9 that specifies pH meter. (Sec VI. Introduction and Sec. VII. A. 2, 9th bullet)
- Process validation of percent recovery should refer only to "add-on" leukoreduction filters. (Sec. VI. B. 2nd bullet)
- Process validation for bacterial contamination testing systems is outside the scope of this document. It should be performed, but not as an element of plateletpheresis validation. (Sec VI. B. 2nd bullet)
- Section IV. D. 1st bullet states that product performance qualification should be completed for each automated blood cell separator in use. Red Cross agrees that installation qualification and operational qualifications are appropriate for each piece of equipment in use, but performance qualification is only performed on each type of equipment.
- The rationale for requiring residual WBC counts within 24 hours of collection is not clear. Components collected on devices with in-process leukoreduction are sufficiently leukoreduced that there is no benefit to product quality or safety by performing this test within 24 hours of collection. In addition, taking the WBC sample concurrently with the bacterial detection sample or the final QC sample reduces the number of entries into the component container and the risk of contamination. (Sec VI. D. 4th bullet)
- The rationale requiring qualification of components at 1/3, 2/3 and 3/3 of expiration is not evident. (Sec VI. D. 6th bullet)
- Table 1 of the Draft Guidance (Sec. VI. D.) is confusing:
    - Is the pH requirement 6.0 or 6.2?
    - Collection performance qualification criteria are based upon final product characteristics; in-process material need not meet the stringent acceptable volume criteria.
    - How often must the product be re-weighed to verify volume? It appears that FDA is requiring the product to be weighed at 3 different times.
    - Must residual WBC counts be performed on both the collection bag and the container bags? If both (or all three) container bags pass, the residual WBC in the collection bag is irrelevant.
    - The 99%/99% target for bacterial testing vs. 0 allowable process failures is confusing.
- Section IV. D introduction, as well as the May 1996 "Recommendations and Licensure Requirements for Leukocyte-Reduced

Blood Products" states that the acceptable criterion for labeling as leukocyte reduced is a residual WBC count <5 x 10e6. Does FDA intend to require the actual count or is it sufficient only to demonstrate that a component meets this qualitative standard?

- Does FDA have data to support what appear to be very narrow acceptance criteria for the volumes of doubles and triples? (Table 1, Sec. VI. D.)
- The need and extent for re-qualification or revalidation following a deviation should be determined according to the establishment's CAPA system; the draft should make reference to the CAPA system rather than define when revalidation should occur. (Sec VI. E.)

Section VII: QUALITY ASSURANCE AND MONITORING

- The draft guidance seems to extend the requirement in 21 CFR 606.100(b) (9), which addresses only investigation of adverse reactions in donors, to include procedures specifying medical intervention for the management of specific types of reactions. Is this FDA's intent?(Sec. VII. A. 2. 2nd bullet)
- The draft seems to allow modification of the collected product to bring it into alignment with final storage conditions; i.e., remove plasma if necessary. What is the time limit when this adjustment can be made? (Sec. VII. A. 2. 6th bullet)
- The draft states that the "actual platelet yield" should be provided to the transfusion facility. Providing the platelet yield to the hospital is usually unnecessary and not useful to the hospital or transfusing physician. Platelet yield should be available to the transfusion facility on request. (Sec. VII. A. 2. 7th bullet)
- The term "total volume loss" seems incorrect. Does FDA really mean "total volume" or "total plasma volume?" (Sec. VII. A. 2. 11th bullet)
- The term "in-process leukoreduction filter" should be replaced with the more accurate "in-process leukoreduction technology." Later in the draft the term "automated leukoreduction methodology" is used; we suggest consistency in terminology. It is not clear why FDA is addressing leukoreduction filters in this document. Does this description allow the addition of an in-line filter if the automated leukoreduction methodology fails? (Sec. VII. A. 2. 12th bullet)
- It is unclear when the requirement for placing the "final component volume" on the label would be applicable and what constitutes reasonable limits. After processing is completed, the product is labeled and subsequently reviewed by quality processes to become available for release. The sample for quality control is removed after labeling, within 24 hours of distribution. Does FDA intend that the product should again be re-weighed and the label modified? 21 CFR 606.121 (c) (6) specifies volume accuracy within 10%. (Sec. VII. A. 2. 16th bullet)
- The donor monitoring requirement for platelet counts less than 100,000/ul is inconsistent with manufacturer's instructions for at least one 510(k) cleared collection device. (Sec. VII. B. 1.)
- The donor monitoring requirement to notify the Medical Director when a post-count is less than 100,000/ul provides no further guidance as to what the Medical Director should do with this information or whether the donor should be notified. This seems

to be unnecessary since the course of action is to defer the donor until the count rises about 150,000/ul. (Sec. VII. B. 1.)

- The sentence beginning, "In particular, before a subsequent donation by a donor who reported an adverse reaction…." is vague. Must the record be reviewed only when the donor has a reaction, or when any one of the specified criteria occurs? Must the Medical Director review every adverse reaction, including those considered "mild"? (Sec. VII. B. 2.)
- The sentence, "In addition you should monitor donors undergoing frequent multiple component collection of Platelets, Pheresis for platelet recovery" requires more specific information. Other than platelet count, what must be monitored? If a pre-collection platelet count is performed on each donation, and it remains above 150,000/ul, what more must be monitored? (Sec. VII. B. 2.)
- The paragraph titled "Total plasma volume loss per 12 months" should clearly state "previous" 12 month period. (Sec. VII. B. 3.)
- The description of "actual platelet yield after collection" seems to indicate that total volume and yield must be re-determined after initial QC sampling, bacterial sampling, etc, even though the component is not ready for release. Is this FDA's intent? (Sec. VII. C. 1.)
- The sentence, "residual WBC count on all collections that do not utilize an automated leukocyte reduction methodology" seems to suggest that residual WBC counts are not required for products collected using an automated leukoreduction methodology. Is this FDA's intent? (Sec. VII. C. 1.)
- Having a guidance requirement for the number of units to be tested that exceeds the requirement of 21 640.25 may be confusing. FDA should utilize the rulemaking process to modify 21 CFR 640.25 to reflect current FDA thinking. (Sec. VII. C. 2.)
- Regarding the statement "As part of your QC protocol you should include testing of components collected on each individual automated blood cell separator device," ARC believes that FDA's intent is that there should be a random selection from products collected on every device. If testing only 4 per month, it might not be possible to test products from each device. (Sec. VII. C. 2.)

Section VIII: PROCESSING AND TESTING

- The expiration dating for Platelets, Pheresis when the integrity of the hermetic seal is broken seems misleading. This section specifies that the expiration date is 24 hours after the seal is broken. 21 CFR 606.122(1) (2) specifies that administration of the product should be "not more than 4 hours after entering the container." (Sec. VIII. C.)

Section IX: LABELING

- By placing the requirement that "the actual platelet yield of each component should be made available to the transfusion service" in the section titled "Labeling" implies that FDA is suggesting that this information be placed on the component label

or on a tie tag. FDA needs to provide additional guidance regarding the placement of this information on the label. Red Cross believes that this could be construed to be an unsubstantiated comparative labeling claim of higher quality or efficacy. A component that meets the regulatory standard is equivalent to all other similarly labeled components.
Section X: REPORTING CHANGES TO AN APPROVED BIOLOGICS LICENSE APPLICATION
• The document does not seem to consider the use of automated equipment intended to be used in a mobile setting when requiring supplements for specific facilities (Sec. X. A. 2nd bullet). FDA needs to re-think its approach to BLA submissions for collection facilities that operate mobile plateletpheresis operations, when multiple of such facilities are under the control of a licensed establishment utilizing the procedures and training methods. • The description of the development and routine review of a Comparability Protocol is outside the scope of this guidance and should be included in "Guidance for Industry: Changes to an Approved Application: Biological Products (July 1997)" (Sec. X. A.) • The requirement to submit only two months of quality control data for BLA supplements seems "out of sync" with quality control requirements elsewhere in the Draft Guidance. Although quality control results are currently monitored on a monthly basis, if FDA intends to move to scan statistics, then two complete "windows" would seem more appropriate. (Sec. X. C. 1. 4th bullet) • In light of FDA's new approach to quality control monitoring, it seems pointless to request the submission of components from only two collections for FDA quality control testing. (Sec. X. E.)

Long-Term Plateletpheresis and Donor Platelet Counts

The 2005 FDA draft guidance, *Collection of Platelets by Automated Methods*, seeks to restrict platelet donations to a maximum of 24 Platelets, Pheresis components in a 12 month period and to limit the interval between donations based upon the total number of products collected. There are few published data to support such a change which can be reasonably expected to significantly restrict the available supply of transfusible platelets, increase healthcare costs and potentially harm recipients awaiting a product delayed because of inadequate supplies. An analysis of American Red Cross system data shows that 3,896 donors (4% of our donors) provided more than 24 platelet components in calendar year 2004, yielding 129,290 distributable products for patients in need. Had the new guidance restricted these donors to 24 platelet components per year, the American Red Cross would have been unable to provide 35,786 products (~6% of distributable products) unless it recruited at least an additional 5799 donors (to increase the donor pool by ~6%) to make up this difference. Additional product losses from donor dissatisfaction resulting from increasingly complex scheduling requirements at predictably busier donor centers could exacerbate platelet deficits throughout the system.

A number of studies have demonstrated that multiple plateletphereses over 3-12 years do not result in significant differences in donor platelet counts vs. controls (Heal JM, et al. *Vox Sang* 1983;45:14 – Matsui Y, et al. *Transfusion* 1986;26:446 – Prior CR, et al. *J Clin Apher* 1991;6:69 – Offner R, et al. *Beitr Infusionsther Transfusionsmed* 1994;32:341) and that 5-15 daily or alternate day donations have no apparent adverse effects upon donors (Glowitz RJ, Slichter SJ. *Transfusion* 1980; 20:199 – Rock G, et al. *Vox Sang* 1992; 63:102). There are no definitive reports to support a hypothesis that platelet donation in excess of 24 products per year is harmful to donors or that donation frequency influences donor safety. Recent data suggest that there is no deleterious increase in stem cell turnover in long-term apheresis donors, despite transient increases in thrombopoietin and circulating CFU-Mk (Scheding S, et al. *Transfusion* 2003; 43:1089 – Wagner T, et al. *Vox Sang* 2001; 81:167). A more recent report that attempted to address the issue of the effects of repeated plateletpheresis (Lazarus et al., *Transfusion* 2001; 41:756) employed a simple difference between the first & last available platelet counts to establish trends, with significantly shorter intervals between control count determinations versus those of the donors. The report also did not examine the effect of donation yield (single, versus double versus triple products) on donor platelet counts. It concluded that "clinically significant thrombocytopenia is unusual when rigorous ongoing review and prudent deferral policies are established and followed." Extensive experience under the 1988 Guidance allowing 24 collections per year in concert with donor deferral for counts $\leq$150,000/μL has established the safety of the current maximum component number and frequency of platelet collection.

The Red Cross has attempted to quantify the experience of its frequent donors. One region has maintained an apheresis donation database since July 1997 (Vassallo and Murphy, in preparation). From 10,474 donors with over 82,374 successful collections through October 2005, 909 individuals who had provided 25 or more total donations were identified. To minimize errors associated with the use of only 2 platelet determinations

to estimate trends in donor counts, a regression line describing each of the donors' pre-procedural platelet counts versus date of donation was constructed (Fig. 1). This yielded a bell-shaped curve of average yearly rates of change (Fig. 2). The mean (±SD) increase in platelet count was 260 ± 6,280/μL per year with a median increase of 540/μL per year. No statistically significant relationship was noted for the calculated rates of change in donor platelet counts for individuals providing <10, 10-19.9, 20-29.9 or ≥30 products per year (Fig. 3). The region's aggregate platelet counts experienced small but quite significant declines during a switch from Baker 9110 cell counters to Cell Dyne 3700 counters in April 2003 and during a Cell Dyne recalibration in January 2005. To minimize the effects on platelet count of different cell counters, seasonal variability (small increases associated with cold weather) or unpredictable changes due to intercurrent medical conditions, a group of 375 donors with donations spanning at least 7 years was chosen for subanalysis of yearly changes in platelet counts versus the number of products they provided per year (Fig. 4). No relationship was evident between the rate of change in platelet count and the number of products donated (or the absolute number of platelets donated per year [data not shown]).

To characterize further the outcome of high frequency donors, six ARC regions provided data on 116 donors, each of whom had donated a minimum of 20 times in 2002 (Notari et al, in preparation). Information on donor platelet counts and component yields was collected for each donation from January 2002 through October 2005, and the average rate of change in donor platelet count was calculated by regression analysis (Fig. 5). Donors were subclassified based on their average number of donated products per year (≤24, 25-36 and ≥37) and the results replotted (Fig. 6). These donors demonstrate a rate of change that is clustered around a mean of minus 3,900/μL per year, a clinically insignificant change. Some donors apparently experienced platelet count declines more than 2 standard deviations from the group mean. This higher rate of decline is independent of the number of components collected, as similar percentages of individuals donating an average of ≤24, 25-36 or ≥37 components in 12 months showed decrements this far from the mean. The long-term hematological significance of such declines in these "higher frequency" donors is unknown. No comparable control data are available and it may be that this decline is related to the shorter duration of observation and lower total number of determinations for many of these individuals, allowing confounders such as different cell counters, seasonal variability and intercurrent donor issues, e.g., viral illnesses or iron deficiency, to produce outliers.

There is currently no way to identify any subgroup of donors predisposed to platelet count decrements with apheresis; however current safeguards guarantee that these donors will not suffer immediate harm. There is certainly a need to study the long-term consequences of plateletpheresis in frequent donors. Given the lack of published evidence demonstrating harm or refuting the safety of long-term repeated platelet donation, the FDA should sponsor a workshop on this subject and encourage the accumulation of prospective data prior to setting unnecessarily restrictive guidances that would negatively impact platelet availability and patient safety.

Figure 1. **Platelet count versus time for a representative donor. The slope of the red regression line is +1.1/μL/day, or about +400/μL/year. Since donor counts can vary up to ~70,000/μL from one determination to the next (Buckley MF, et al. *Thromb Haemost* 2000; 83:480), this method more reliably characterizes a donor's platelet counts over time. Here, the Oct. 1997 initial count of 239,000/μL could have been paired with the Oct. 2002 count of 171,000/μL or the Dec. 2002 count of 286,000/μL, had either of these been the donor's last available count (respectively, a fall of 14,000/μL/yr or rise of 9,000/μL/yr). Simple arithmetic determinations are more vulnerable to a number of confounders, while this more robust method clearly demonstrates no significant change in this donor's platelet count.**

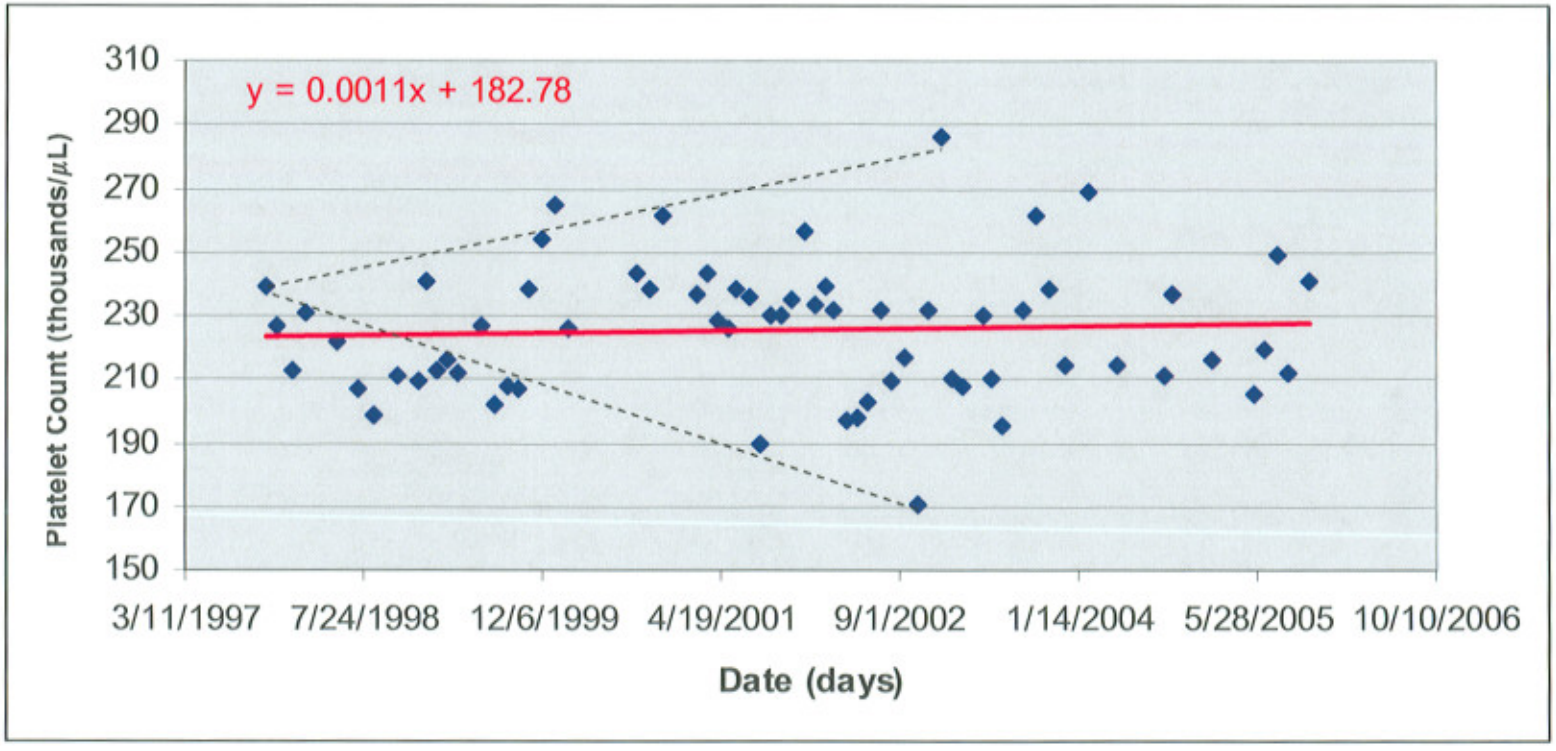


Figure 2. **Histogram of derived average yearly change in 909 donors' platelet counts (mean 13.4 [range: 3-40] products donated per year; mean 5.9 [range: 1.2-8.3] years of donations)**

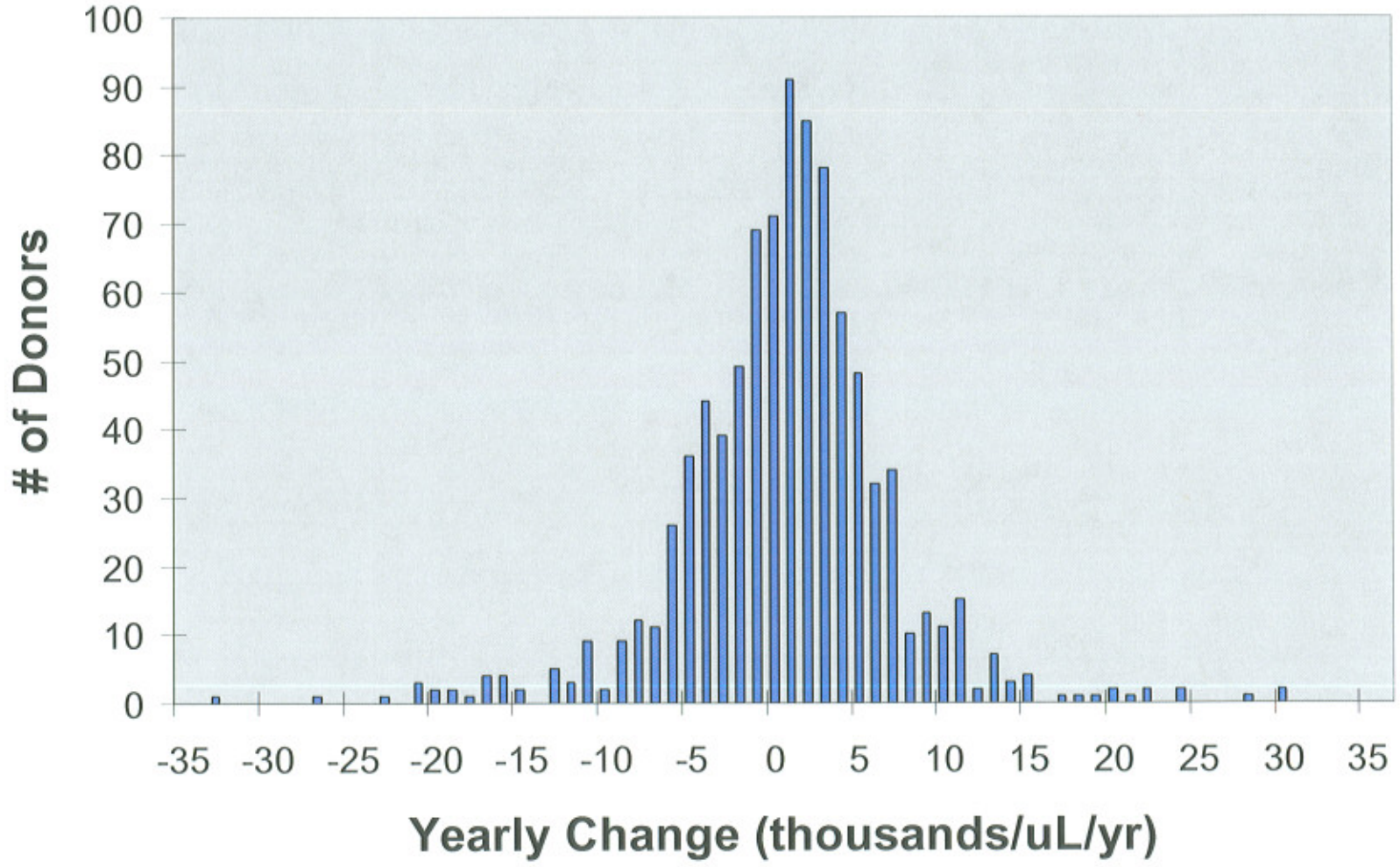
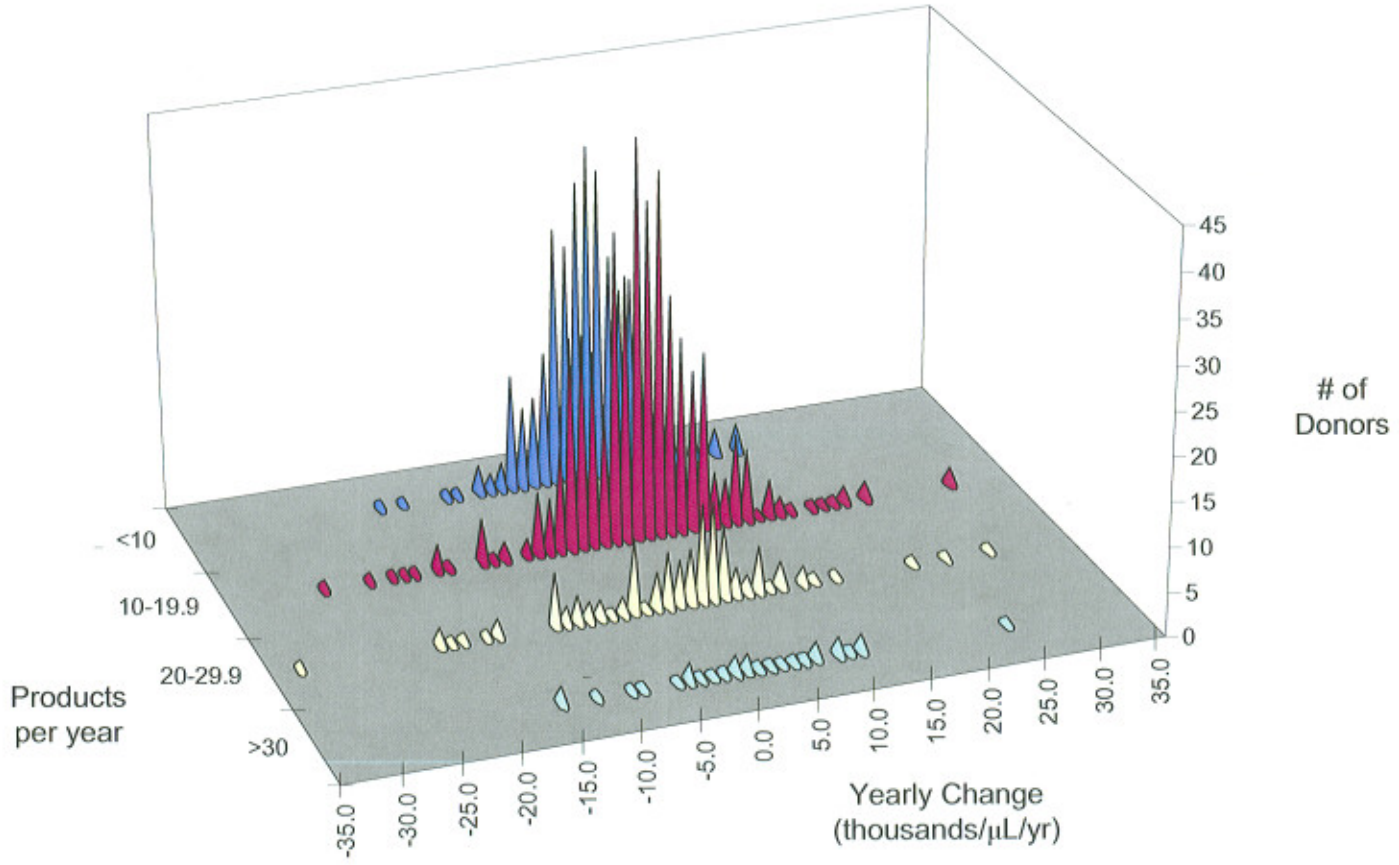


Figure 3. Histogram of derived yearly changes in 909 donors' platelet counts separated by ranges of products collected from each donor per year.



	<10	10-19.9	20-29.9	>30
Mean change	0.26	0.56	-1.07	0.61
SD	4.41	6.47	8.92	8.70
Median change	0.42	0.70	0.35	0.44
n	323	451	107	28

Figure 4. Yearly change in platelet counts for 375 individuals with donations spanning at least 7 years

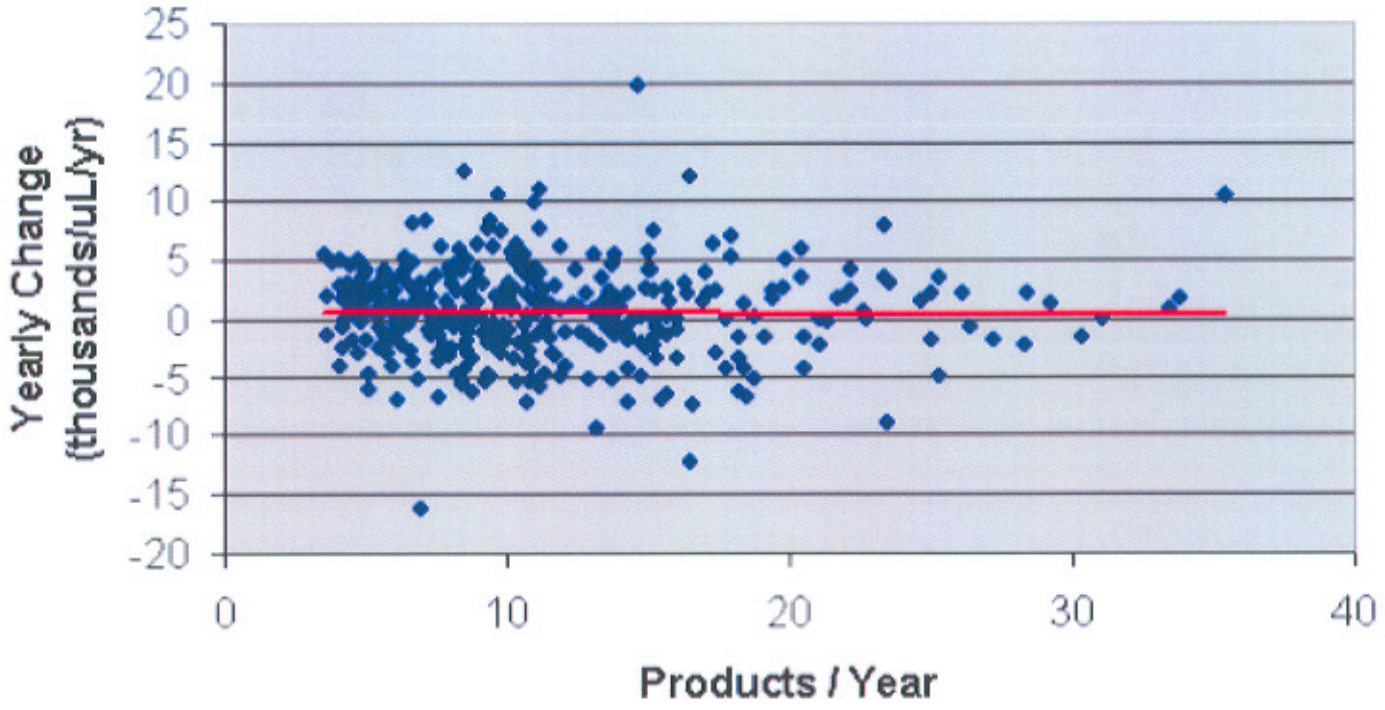


Figure 5. Histogram of average yearly changes in 116 high-frequency donors' platelet counts.

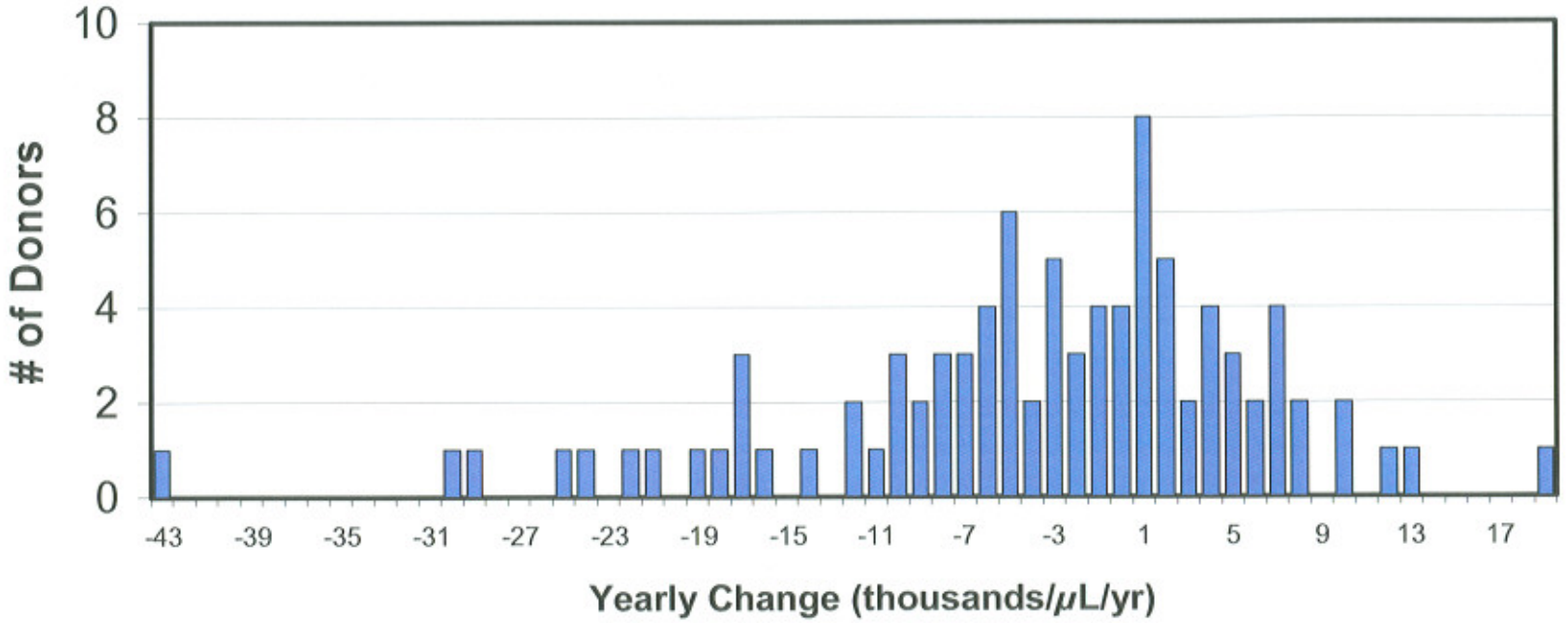


Figure 6. Histogram of average yearly changes in 116 high frequency donors' platelet counts separated by ranges of products collected from each donor per year.